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Determining the optimal stockpile level for combination vaccines

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by

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Abstract

By 2015, vaccine shortages still remained one of the major problems around the globe, as described in the annual secretariat report of the Global Vaccine Action Plan (GVAP). Despite multiple initiatives to reduce vaccine shortages, supply interruptions are unexpected and unavoidable. To mitigate the risk of such interruptions, vaccine stockpiles have traditionally been the tool of choice. However, the models used to determine vaccine stockpile levels have only considered the use of monovalent vaccines, which provide protection against a single disease. This study aims to determine optimal stockpile levels for combination vaccines, which provide protection against multiple diseases. First, through discrete event simulation, we explore the effect on antigen shortages while maintaining stockpiles of multiple vaccines from multiple suppliers with different reliability conditions. We consider policies that mimic those of a decision maker that can either use vaccines with the most or the least reliable supply to set up the safety stockpile. Second, we propose a stochastic tractable safety stock model that considers the availability of a pool of monovalent and combination vaccines in the stockpile. Finally, we contrast the recommendations from the simulation with those from the stochastic safety stock model, and we analyze the effect of having a mix of combination and monovalent vaccines to mitigate the shortage risks for any given antigen.

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1. Introduction

In 2010, international health organizations such as the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the National Institute of Allergy and Infectious Diseases (NIAID), the Bill and Melinda Gates Foundation, and other partners collectively launched the 'Decade of Vaccines' collaboration program [1]. This program includes the Global Vaccine Action Plan (GVAP) for the years 2011 to 2020, which aims to immunize every child and woman irrespective of their location or economic condition [1]. One of the six strategic objectives of GVAP is that every immunization program conducted in each country should have a sustainable vaccine supply [1]. In 2014, during the annual assessment of the GVAP goals, the Strategic Advisory Group of Experts on Immunization (SAGE) claimed that the goal of attaining target global immunization coverage rates for multiple vaccines was off track. One of the main reasons for this was vaccine stockouts due to global supply interruptions [2].

Table 1: Global vaccine stockout details

	2010	2011	2012	2013	2014
Countries facing minimum one national-level stockout for at least one vaccine	67	66	57	54	50
Number of stockout events in a year	153	148	120	111	110
Average number of stockout events per year per country	2.28	2.24	2.11	2.06	2.2
Average duration of a stockout event (in days)	45.2	35.3	34	32	52.7

Sources: GVAP—Monitoring, Evaluation, and Accountability—Secretariat Annual Report 2015 [2].

Table 1, illustrates the number of stockout events that occurred globally between 2010 and 2014. On average 58 countries faced stockouts every year between 2010 and 2014. In 2014, out of 194 countries, 50 countries faced national-level stockouts at least once a year [2]. Most of the countries facing stockouts were low- to middle-income developing countries [2]. These supply interruptions have an impact on global immunization coverage rates [2], which can cause the risk of spreading diseases that have been previously controlled.

All countries are susceptible to supply interruptions and vaccines shortages. In the U.S., over the past decade, there was on average one pediatric vaccine interruption per year. The duration of these vaccine shortages varied widely from three months to 22 months (see Table A [3]–[9] in the Appendix). Hence, it is reasonable to expect that the developing countries with weaker healthcare systems than that in the U.S. may face at least as many vaccine shortages with similar or lengthier duration. Evaluation of the safety stocks to mitigate vaccine shortages requires careful consideration, as decision makers in developing countries need to balance costs and their ability to maintain safety stocks in limited cold-chain facilities.

Most of the available literature on safety stock levels of vaccines considers safety stocks composed solely of monovalent vaccines, which provide protection against single disease in one shot, whereas combination vaccines provide protection against multiple diseases in one shot. Additionally, the vaccine stockpile literature does not consider the case when there are multiple suppliers for a vaccine, while in reality UNICEF, the Global Vaccine Alliance (GAVI), and WHO try to maintain competition among suppliers to avoid supplier monopolies in the global vaccine markets [10], [11].

This study aims to determine the stockpile levels for combination vaccines facing uncertain supply interruptions when multiple suppliers per vaccine are available in the market. We first develop a simulation model to mimic supply shortages under different stockpile configurations and explore the effect of these configurations on the shortage levels resulting from different supply interruption scenarios. Second, considering the results of the simulation study, we propose a tractable safety stock model. We compare the recommended safety stock levels from the tractable model with those resulting from the simulation study.

The remaining document is divided into four main sections. Section 2 provides a literature review; Section 3 details the research question and the hypothesis of this study; and Section 4 describes the methodology, which includes simulation study and the formulation of the proposed tractable safety stock model. Section 5 describes the validation of the safety stock model, and finally, Section 6 provides concluding remarks and future extensions.

2. Literature Review

This section provides an overview of the different approaches used to determine the vaccine stockpile levels used to mitigate shortages. Most of the studies reviewed focus on the safety stock levels for monovalent vaccines [8], [12]–[14], which is inadequate as most countries use combination vaccines in their immunization schedules. However, studies that consider combination vaccines [7], [15] fail to consider either the uncertainty in the occurrence of supply interruption and assume that the length of the supply interruption is deterministic in nature.

In the U.S., the pediatric vaccine stockpile maintains a rotating stock for all its recommended vaccines. By law, the country maintains a stock to satisfy six months of the vaccine demand carried out through the Vaccines for Children (VFC) program [15]. The six months of the VFC demand represents only three months of the national demand [16]. However, these prescriptive stockpile levels were inadequate to deal with the vaccine supply interruptions observed during 2000 and 2012, which lasted up to 22 months [8] (see Appendix Table A for details of shortage events observed in the U.S.).

At the global level, vaccine stockpiles are maintained by international health organizations such as WHO, UNICEF, Médecins Sans Frontières (MSF), and the International Federation of the Red Cross (IFRC). WHO currently maintains stockpiles for four vaccines—the smallpox, meningococcal, yellow fever, and oral cholera vaccines [17]. UNICEF and its partners are currently developing oral polio vaccine (OPV) stockpile [18]. The decision to determine which vaccine should be stockpiled for global use and the number of doses to be stored is made by representatives from WHO and in some cases in combination with MSF, IFRC, and UNICEF [17],[19]. Decisions on each stockpile level are evaluated by discussing different scenarios for each vaccine that considers various factors such as disease characteristics, including fatality rates, frequency of observed epidemics, number of countries affected, availability of disease detection methods, vaccine efficacy, vaccine availability, and the existence of alternative treatment methods [17]. The stockpile levels of the vaccines maintained by WHO and its international partners are shown in Table 2.

Table 2: Vaccine stockpile doses at international health organizations

Vaccine	Establishment year	Doses
Smallpox vaccine	1980	35 million
Meningococcal vaccine	1997	9 million
Yellow fever vaccine	2001	5 million
Oral cholera vaccine	2013	6 million
Oral polio vaccine	In progress	TBD

Sources: [17], [18], [20], [21]

In 2006, Jacobson et al. [8] analytically proposed a stochastic safety stock model that minimizes the risk of a vaccine supply shortage for monovalent vaccines in the U.S. The model identifies adequate stockpile levels for different vaccines, considering that supply interruptions and their lengths are random. The supply was assumed to be gradually restored via two different ramp-up functions [8].

Proaño et al. [13] proposed a multi-attribute utility model to determine the appropriate stockpile level for monovalent vaccines considering the need to minimize cost, maximize herd immunity, and minimize the risk of shortages. The model determines safety stock levels that optimize utility functions for the vaccine shortages, the coverage rate, and the financial cost savings.

Shrestha et al. [7] introduced ‘VacStockpile,’ a spread-sheet and rule-based tool, to evaluate the impact of stockpile levels with six months of supply in the U.S. The tool suggests the number of children that will not receive the recommended doses of vaccine for given stockpile levels, considering the likelihood of a finite set of shortage scenarios [7]. The model also defines the cost associated with maintaining these stockpile levels considering a finite set of monovalent and combination vaccines in stock. However, for combination vaccines, VacStockpile simply facilitates the evaluation of all permutations of different likely shortage scenarios and does not pre-emptively provide the stockpile levels to be maintained against random supply interruption [16].

Truong [22] derived upper and lower bounds for the target stockpile levels for monovalent and combination vaccines. The stockpile policy given by Truong [22] is based on a marginal cost analysis approach considering non-linear backorder cost with uncertainty in the fulfillment of placed orders. The model is then verified by observing the results of 1,000 random instances of these scenarios. The study also shows that there is a significant decrease in stockpile level if there is more than one supplier for any particular vaccine [22]. The holding and backorder costs vary widely among countries, and it may not always capture the risk of supply interruptions appropriately.

Thompson and Tebbens [23] proposed a framework for optimal global stockpiles in the form of a stock and flow diagram. The framework guides in determining the trade-offs between vaccine stockpile cost and health benefits considering the vaccine stockpile to be used during the emergency response to a disease outbreak [23]. The framework also highlights the need for improving global vaccine supply efficiency to ensure an adequate vaccines supply and provides recommendations for universal vaccines (vaccines having large global demand) and non-universal vaccines (new and niche vaccines) [23]. It does not propose a tractable model to determine the optimal stockpile levels and also does not consider the existence of multiple vaccines providing similar antigens that can satisfy the demand of antigens.

3. Research Question

In this study we aim to determine what the optimal stockpile level should be for vaccine safety stocks that contain combination vaccines to mitigate the risk of uncertain supply interruptions while considering the presence of multiple suppliers having different likelihoods of supply interruptions. We also aim to determine the impact on safety stockpile levels of choosing to stock vaccines with a high risk of supply interruptions versus using vaccines with a low risk of supply interruptions. Without loss of generality, we refer to the first alternative as the policy of stockpiling risky vaccines and to the second as the policy of stockpiling robust vaccines.

To achieve the aforementioned objectives, we apply our proposed methodology to the experimental scenarios designed to consider the needs of low-income (LI) and lower-middle-income (LMI) countries served by the WHO African region, which has suffered frequent supply interruptions, as observed in the 2015 GVAP secretariat report [2],[24],[25]. In particular, we focus on the safety stock of vaccines offering the diphtheria-tetanus-pertussis (DTP), haemophilus influenzae type B (Hib) and hepatitis B (HepB) antigens. Such vaccines include monovalent vaccines—DTwP, Hib, and HepB—and the combination vaccine DTwP-Hib-HepB, usually referred as the pentavalent or penta vaccine.

4. Methodology

We approach the research problem by first understanding the trends in supply shortage levels of a vaccine as a result of changes in the market conditions through a simulation study. We then apply that which was learned from the simulation study to develop a prescriptive tractable safety stock model. Section 4.1 explains the simulation study in detail, while section 4.2 details the tractable safety stock model.

4.1 Simulation Study

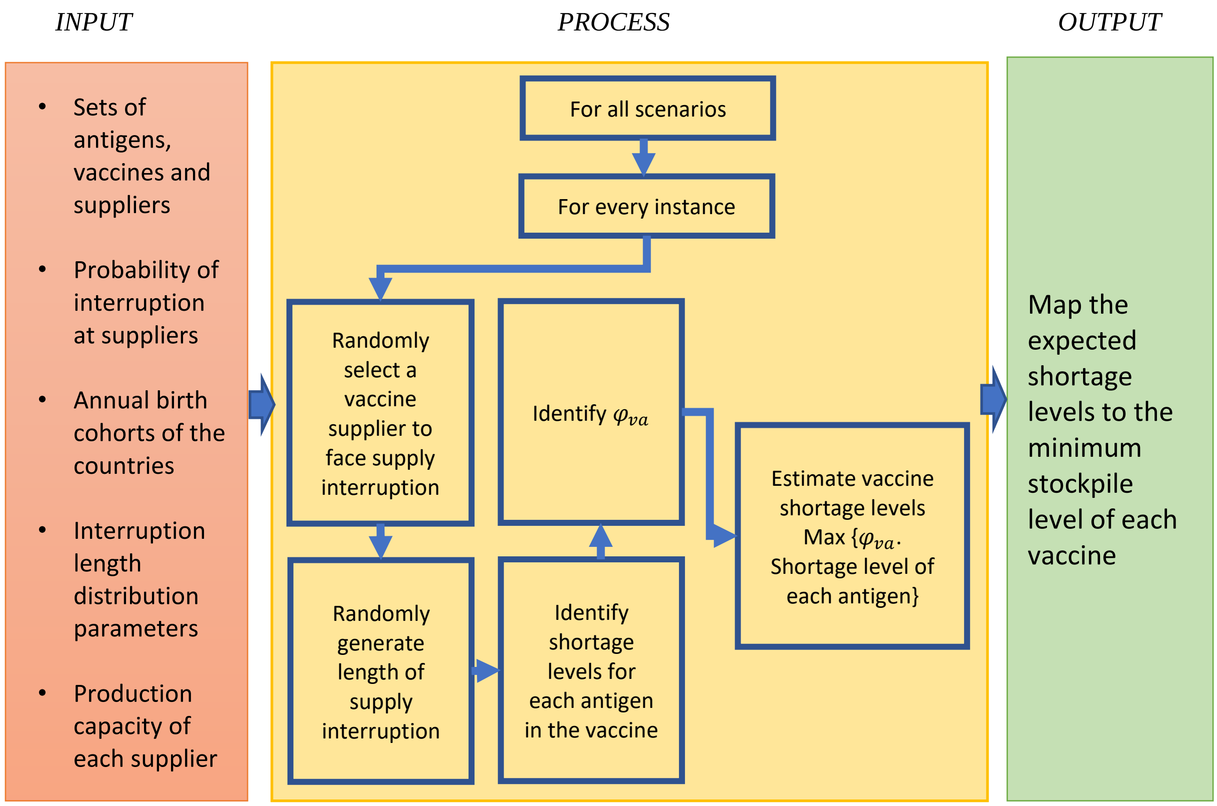
We propose a discrete simulation model to mimic different shortage scenarios by considering multiple input factors. This simulation model is used within an experimental design to test the effect of the following factors: (1) the number of vaccine suppliers, (2) the probability of supply interruption for these suppliers, (3) the length of the supply interruption, and (4) the choice of stockpiling policy (i.e., using risky vaccines vs. robust vaccines). In section 4.1, we will first describe the overview of the proposed simulation model and then explain in further detail the structure of the experimental design along with the set of assumptions considered in our experimentation as well as in the tractable model proposed in section 4.2.

4.1.1 Simulation Model

The simulation model mimics the shortage scenarios based on the different inputs and determines the expected shortage levels for each of the vaccines constituting the safety stock. The simulation model evaluates shortage levels that could happen over a planning horizon of one year for randomly generated instances of supply interruptions. The simulation assumes that the impact of a vaccine supply interruption can be mitigated by the use of alternative vaccines (some of them being combination vaccines) that provide some or all of the antigens missing due to the vaccine shortage. The simulation model consists of two random events: one that determines whether a vaccine will face a supply interruption and, if so, the random length of such interruption.

Figure 1 illustrates the flow of this simulation model. First, the model randomly determines which vaccine supplier will undergo a supply interruption based on their probability of having a supply interruption. Then, the model randomly determines the length of such interruption based on a given distribution. Then, the shortage level for all the antigens provided by the vaccine facing a supply interruption is determined. The resulting deficit of the number of antigens serves as a proxy of the expected antigen shortage, which is satisfied by all the vaccines in the safety stock that can supply the antigen of the vaccine in shortage.

The study is conducted using birth cohorts and the immunization schedules of 28 LI and LMI countries in WHO's African region (see Appendix Table B) [24],[25]. The vaccine immunization schedules were obtained from the 'WHO Vaccine-preventable Diseases: Monitoring System, 2016' [26], and the annual birth cohorts for the countries were obtained from the 'UNPD Population and Demographic Data Estimates (Medium Variant), 2015' [27].



φ_{va} = Proportion of antigen 'a' demand satisfied by vaccine 'v'

Figure 1: Simulation model process flow chart

As described in Figure 1, the model inputs include the set of vaccines, the set of antigens supplied by those vaccines, the set of suppliers of each vaccine, the probability of interruption at each supplier, the distribution of the interruption length, and production capacities. The inputs are provided to a model based on the experimental scenario that we want to test. Each experimental scenario is replicated 1,000 times. We assume that if there are n vaccines supplying antigen a and each vaccine has m suppliers, then the total production from these suppliers is equal to the total requirement of antigen a in the market. Only in cases when there are only combination vaccines in the market and some of the antigens contained in the vaccine have a higher number of recommended doses than remaining antigens, it is possible to have some surplus for the antigens with lower dose requirements. We assume that both combination vaccines and monovalent vaccines are offered in the market, yet a major portion of antigen demand is satisfied via combination vaccines.

For a vaccine v supplying a set of antigens a_v, the simulation first determines whether there will be a supply interruption at any of its suppliers based on their probability of interruption, which is assumed to be independent from the probabilities of interruption for other suppliers. Then, a second random event takes place that determines the length of the supply interruption (in days) for those vaccine suppliers. Interruption length accounts for the time from the beginning of the supply interruption until that supplier is back to full production, and during this interval the production from the supplier is assumed to be completely halted—that is, no partial production levels are considered in this study. It is assumed that the length of an interruption follows a known distribution, whose parameters are provided as inputs to the model and can be varied based on the experimental scenario that we test. A truncated normal distribution is considered as a preliminary choice to explore the effect of interruption length on shortage levels. A lead time of seven days is assumed necessary to account for shipping the vaccines from the supplier to the final destination once the random interruption is over.

After the random interruption length is determined, the model quantifies the shortage levels for each antigen a_v resulting from the vaccine in shortage. The shortage level is identified by mapping the unmet antigen needs of the population over the period of interruption. The unmet antigen need is determined by comparing the antigen demand versus the supply provided by all vaccines containing that antigen during the supply interruption. The antigen demand is computed from the daily number of births in the population and number of antigen needed per child to be fully immunized. The notation described below and equation (1) provide the mathematical representation of antigen demand during the interruption period.

Let,

A: Set of antigens
V: Set of vaccines articulated to supply all the antigens
S: Set of vaccine suppliers
S_v: Set of suppliers for vaccine $v \in V$. $S_v \subset S$
V_a: Set of vaccines containing antigen $a \in A. V_a \subset V$
A_v: Set of antigens supplied by vaccine $v \in V$. $A_v \subset A$
L: Length of supply interruption in days.
d_a: Daily demand of antigen $a \in A$ doses.
C_{sv}: Daily supply of vaccine $v \in V$ produced by supplier $s \in S$
N_a: Need of antigen $a \in A$ during interruption period.
m_v : Number of suppliers of vaccine $v \in V$.
p_v : Probability of interruption for suppliers of vaccine $v \in V$.
W_{va}: Relative importance of vaccine $v \in V$ with respect to supply of antigen $a \in A$.

Sup_v : Total supply of vaccine $v \in V$ per day.
I_v: Supply shortage level of vaccine $v \in V$.

When there is a supply interruption at supplier s_v, then supply per day of the vaccine from that supplier C_{sv} is stopped for the length of the supply interruption. Therefore, the need for antigen a across the population during the supply interruption of vaccine v is given by

$$N_a = L * \left(d_a - \sum_{\substack{s \in S_v \\ v \in V_a}} C_{sv} \right) \qquad \forall\, a \in A \ . \qquad (1)$$

The expected shortage level of each vaccine is determined such that the antigen need of each antigen a identified in (1) is fulfilled completely by the vaccines v_a containing antigen a, which may be provided by different suppliers. Considering that the proportion of demand for antigen a supplied by vaccine v is expressed as φ_{va}, then the antigen needs N_a for antigen a when a vaccine is in shortage is fulfilled by all other vaccines supplying that antigen in the proportion given by φ_{va}. Thus, for a vaccine that contains multiple antigens, the expected vaccine shortage level I_v is defined as the maximum of the number of doses required to fulfill the need for the antigen supplied by that vaccine.

$$I_v = \ max(N_a * \ \varphi_{va} | a \ \in \ A_v) \qquad \forall\, v \in V \qquad (2)$$

The ratio φ_{va} is estimated by the relative importance W_{va} of the vaccine v toward the safety stock with respect to the overall relative importance of all other vaccines supplying antigen a, as shown in (3).

$$\varphi_{va} = \frac{W_{va}}{\sum_{v \in V_a} W_{va}} \qquad \forall\, v \ \in V \ and \ a \ \in A \qquad (3)$$

The relative importance of vaccine v for the supply of antigen a (W_{va}) is higher as the supply of v (Sup_v) is high with respect to the antigen demand d_a. Also, it is higher as the number of suppliers for v (m_v) decreases. Whereas As the probability of interruption p_v is high, W_{va} is higher in case of policy to stockpile risky vaccines but it decreases in case of policy to stockpile robust vaccines. The expression (4) is used for the policy that stockpiles risky vaccines because here W_{va} is directly proportional to the average probability of having a supply interruption. Hence, the relative importance of vaccines for the supply of antigen 'a' increases as their likelihood of having a supply interruption increases. Equation (5) is used for the second policy to stockpile robust vaccines since it considers that W_{va} is directly proportional to the probability of not having an interruption at the vaccine supplier. Hence, the relative importance of vaccines for the supply of antigen 'a' increases as their likelihood of having supply interruptions decreases.

$$W_{va} = \left(\frac{(Sup_v)/_{m_v}}{d_a}\right) * p_v \qquad \forall\ v\ \in V\ and\ a\ \in A \qquad (4)$$

$$W_{va} = \left(\frac{(Sup_v)/_{m_v}}{d_a}\right) * (1 - p_v) \qquad \forall\ v\ \in V\ and\ a\ \in A \qquad (5)$$

4.1.2 Experimental Design

The simulation model described in section 4.1.1 serves as a tool for conducting experiments over scenarios of interest. We consider the set of vaccines that contains antigens for DTP that are part of the immunization schedule of the 28 LI and LMI African countries. According to the 2015 GVAP secretariat report [28], DTP-containing vaccines have faced frequent shortages. We assume that the DTP-containing combination vaccine DTwP-Hib-HepB, also called a pentavalent vaccine, is available in the market along with the three monovalent vaccines DTwP, Hib, and HepB (monovalent vaccines with antigens for DTP, Hib, and HepB, respectively).

We test two stockpiling policies: policy (A)—stockpiling risky vaccines that are prone to supply interruptions and policy (B)—stockpiling robust vaccines that suffer fewer supply interruptions (i.e., that are robust to interruptions). When we have both monovalent and combination vaccines in the market, for a given antigen, the shortage level will be fulfilled by a safety stock containing both types of vaccines. Based on the experimental combinations, each of these vaccine types may have higher or lower probabilities of interruption. So, two different stockpiling policies are tested, first in which the larger fraction of the antigen shortage is fulfilled by the stockpile of vaccines with a higher probability of interruption and second where stockpiling policy satisfies a larger portion of antigen shortage by stockpiling vaccines with a lower probability of interruption. To determine the aforementioned fraction of antigen demand satisfied by each type of vaccine, φ_{va} from (3) is used. Then, to mimic policy A we use expression (4) for W_{va}, while expression (5) is used to mimic policy B. We use 2^k factorial design to test the effect of the parameters related to these four vaccines on their expected shortage levels.

We conduct three sets of experiments. Experiment 1 considers that we have both combination and monovalent vaccines in the market and that the safety stockpile also contains both combination and monovalent vaccines. Some portion of the antigen shortage level is satisfied by combination vaccines, while the remaining portion is satisfied by monovalent vaccines. This portion varies depending upon whether stockpiling policy A or B is used for determining stockpile levels. It also depends on the number of vaccine suppliers and their production capacities. In experiment 2, we consider that the market has only monovalent vaccines and that these vaccines are the only ones used for the stockpile. Hence, for a given antigen during an interruption, its supply is fulfilled by only monovalent vaccines. Stockpiling policies A and B do not play any role as we do not have any alternative combination vaccine in the stockpile to share the antigen shortage level. For experiment 3, it is considered that the stockpile includes only combination vaccines. Even in this experiment stockpiling policies do not play any role as the entire antigen shortage during the supply interruption is satisfied by only combination vaccines in the stockpile. Experiments 2 and 3 aim to facilitate comparing the expected shortage levels of vaccines when we have only monovalent vaccines in the safety stock or only combination vaccines or a mix of combination and monovalent vaccines.

Certain assumptions are needed to support our analysis. It is assumed that for a given vaccine all its suppliers have the same probability of interruption. Also, we assume that for a vaccine, each of its suppliers has equal production capacity. For a given antigen, the total supply of all vaccines containing the antigen is enough to satisfy the uninterrupted antigen demand and yet there is no excess vaccine supply for a given antigen in the market. However, for experiment 3, since there is only pentavalent vaccine in the market to satisfy all antigens' demand and each antigen has different dosage requirements, we allow the over-production of Hib and HepB antigens which require fewer doses than the DTP antigen. For experiment 1, when we have both monovalent and combination vaccines together in the market, it is assumed that a major portion (60–70%) of the antigen demand in the market is supplied by the combination vaccine.

Next, we describe the actual set up for each of the three experiments. We explain how the four factors that we seek to control—that is, the number of vaccine suppliers, the probability of interruption, the mean interruption length, and the stockpiling policy—have been incorporated into each of the three experiments.

4.1.2.1 Experiment 1

In this experiment, we propose a 2^{10}-factorial design resulting from the study of how our four factors of interest affect the safety stockpile of each of the four vaccines, DTwP, DTwP-Hib-HepB (penta), Hib, and HepB. The factors considered in this experiment are a number of suppliers for each vaccine, the probability of interruption at each vaccine's suppliers, the mean interruption length, and stockpiling policy. Table 3 describes the levels for each factor used in this experiment. The 2^{10}-factorial design results in 1,024 experimental scenarios. Each experimental scenario is replicated 1,000 times to generate 1,024,000 random instances of supply interruptions.

Table 3: Factors used in experiment 1

No.	Factors	Level 1	Level 2
Number of suppliers of vaccines			
1	Number of DTwP suppliers	1	7
2	Number of DTwP-Hib-HepB suppliers	1	7
3	Number of Hib suppliers	1	7
4	Number of HepB suppliers	1	7
Probability of interruption at suppliers			
5	DTwP suppliers' probability of interruption	0.06	0.2
6	DTwP-Hib-HepB suppliers' probability of interruption	0.06	0.2
7	Hib suppliers' probability of interruption	0.06	0.2
8	HepB suppliers' probability of interruption	0.06	0.2
Interruption length			
9	Mean interruption length (days)	150	360
Stockpiling policy			
10	Stockpiling policy	A	B

The probability of interruption values for each level shown in Table 3 corresponds to the probability of vaccine supply interruption over a period of one year. These probabilities are estimated for one year considering that the supply interruption happens once in five years (as level 2) or once in 15 years (as level 1). These derived values correspond to 0.2 and 0.06 factor levels for the probability of supply interruption, respectively. From 1985 to 2000 (a period of 15 years), there was no major supply interruption observed in the U.S. [29], while from 2000 onwards to 2012 frequent shortage events are observed, as listed in Table A in the Appendix. Thus, the lower factor level for the probability of interruption is considered as a supply interruption occurring once in 15 years.

UNICEF, GAVI, and WHO have worked toward increasing the number of vaccine suppliers in the global market and avoiding a monopoly by any single supplier. Due to these efforts, DTP-containing vaccines on an average have six

WHO-qualified suppliers in the global market [30]. Hence, a high factor level for the number of suppliers for each vaccine is considered to be seven.

From the 2015 GVAP annual secretariat report [2] and the data shown in Table 1 in the introduction section, it can be seen that the average duration of a stockout was at least two months for 2010–2014. These stockouts are reported when the safety stock for a three-months' supply is depleted [2]. Hence, we can assume that a supply interruption can last for at least five months. However, from the shortages reported in the U.S. in early 2000 (refer Appendix Table A), we see that the supply interruptions lasted for more than a year on average. As we are considering a time horizon of one year for the simulation instance, we assume that the maximum interruption over a year can be 12 months (360 days).

4.1.2.2 Experiment 2

In this experimental set, we consider that the safety stock relies exclusively on three monovalent vaccines, DTwP, Hib, and HepB. The experimental factors in this experiment are the number of suppliers for each vaccine, the probability of interruption at each vaccine's suppliers, and mean interruption length. The list of factors under consideration and the factor levels are given in Table 4. The resulting 2^7-factorial design is used, which results in 128 experimental scenarios. Each scenario is also replicated 1,000 times in the simulation model, giving 128,000 instances of supply interruption. The assumptions and the selection of the factor levels are justified similarly as that for experiment 1.

Table 4: Factor levels for experiment 2

No.	Factors	Level 1	Level 2
Number of suppliers of vaccines			
1	Number of DTwP suppliers	1	7
2	Number of Hib suppliers	1	7
3	Number of HepB suppliers	1	7
Probability of interruption at suppliers			
4	DTwP suppliers' probability of interruption	0.06	0.2
5	Hib suppliers' probability of interruption	0.06	0.2

6	HepB suppliers' probability of interruption	0.06	0.2
Interruption length			
7	Mean interruption length (days)	150	360

4.1.2.3 Experiment 3

In this experiment, we consider that only the pentavalent combination vaccine (DTwP-Hib-HepB) is available in the market and its safety stock to fulfill any antigen's demand from a supply interruption of the pentavalent vaccine. Table 5 shows the factors considered for this experiment and their experimental levels. Here, a 2^3-factorial design is used, resulting in eight experimental scenarios replicated 1,000 times, and thus we have 8,000 instances of supply interruption.

Table 5: Factors used in experiment 3

No.	Factors	Level 1	Level 2
Number of suppliers			
1	Number of DTwP-Hib-HepB suppliers	1	7
Probability of interruption at suppliers			
2	DTwP-Hib-HepB suppliers' probability of interruption	0.06	0.2
Interruption length			
3	Mean interruption length (days)	150	360

4.1.3 Results

We aim to determine whether there are any significant effects of the key factors on the expected shortage and shortage variance for each vaccine under consideration. The expected shortage for a given experimental scenario is computed as the mean shortage level across all 1,000 replications of that scenario, and the variance of the shortage for that experimental scenario is the variance of the shortage levels across the same 1,000 replications. Also, the analysis is performed to determine if there are any differences in expected shortage levels and the costs across experiments 1, 2, and 3.

Experiment 1 includes both combination and monovalent vaccines in the stockpile. We analyze the expected shortage of the individual vaccines as well as expected shortages across all vaccines in the safety stock. Figure 2 illustrates the main effects of all factors on the expected shortage across all vaccines. It can be seen that as the number of suppliers for each monovalent vaccine increases, the total shortage across all the vaccines decreases. However, as the number of suppliers for the penta vaccine increases, there seems to be an increase in the total expected shortage levels. On the other hand, if there is an increase in the probability of interruption at any vaccine supplier, the total expected shortage level increases. Similar is the effect of interruption length. As the mean interruption length increases, the total expected shortage also increases. However, the effect of choice of stockpiling policy on the total expected shortage does not seem to be significant.

Figure 4 shows the main effects plot of the key factors on the expected shortage levels of the individual vaccines. It can be seen that when the number of suppliers of the vaccine under consideration increases, there is a decrease in the expected shortage level. However, if the number of suppliers of a vaccine containing at least one similar antigen increases, there seems to be an increase in the expected shortage level, whereas with the increase in the probability of interruption and the mean interruption length, the expected shortage of all the vaccines increases. Also, there is no effect of a change in stockpiling policy A or B on any of the vaccine's expected shortage levels. Additionally, multiple two-level interactions of the factors seem to have a significant effect on the expected shortage levels of the vaccine, such as number of vaccine suppliers and interruption length, number of vaccine suppliers and probability of interruption for the same vaccine suppliers, and number of suppliers of the vaccine under consideration and number of suppliers of a vaccine supplying similar antigens to those of the vaccine under consideration. Interaction plots for total expected shortage and each of the individual vaccine shortages is shown in Appendix figures A3 and A4.

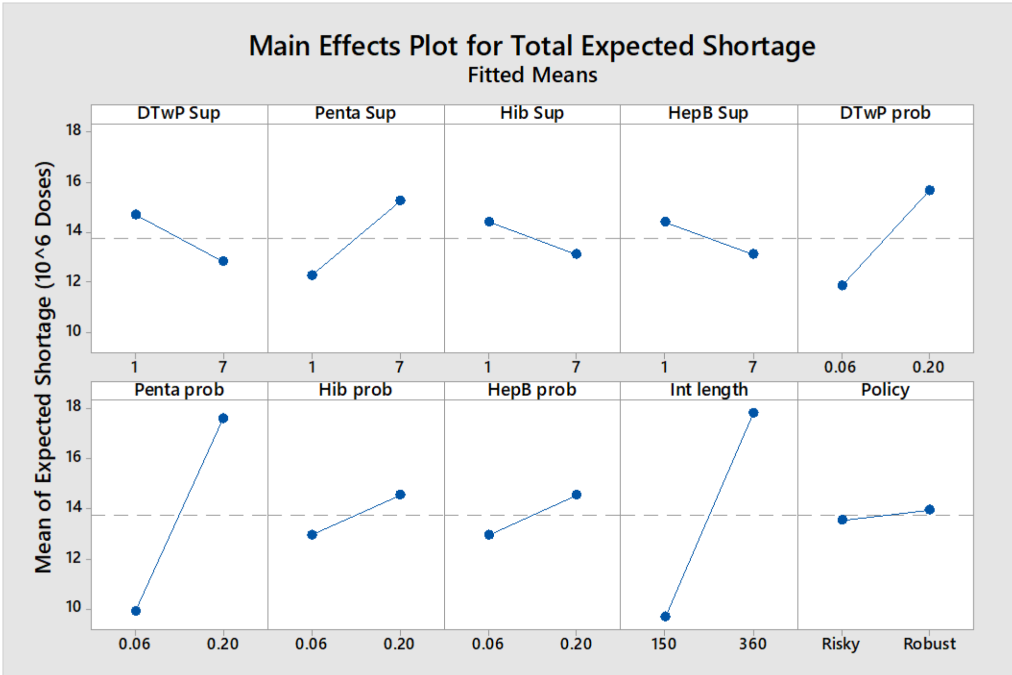


Figure 2: Experiment 1—Main effects of factors on total stockpile levels

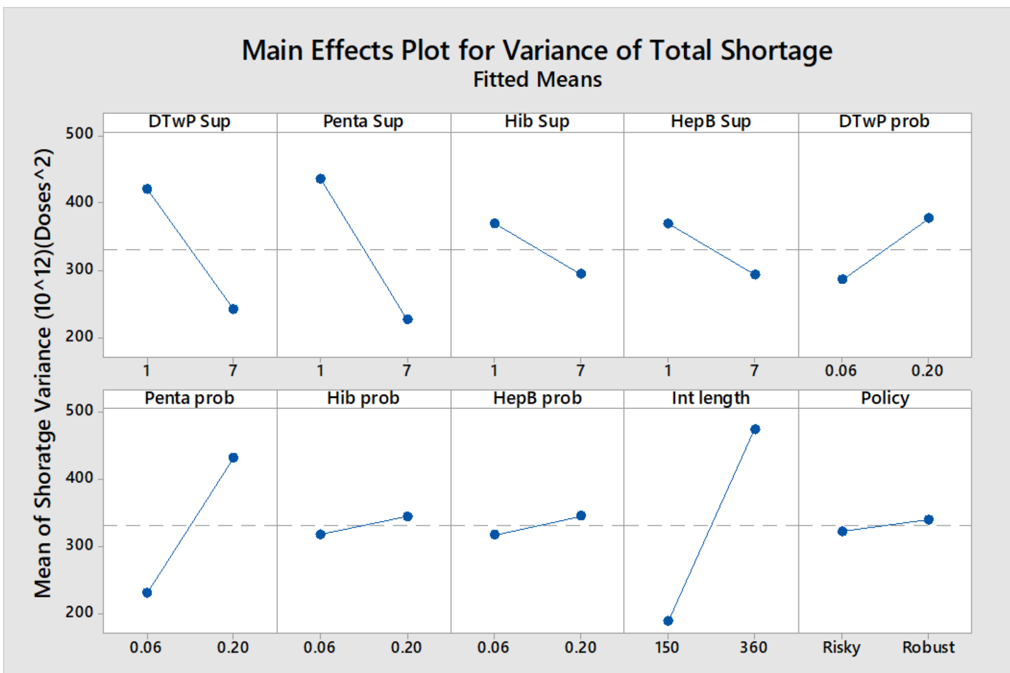


Figure 3: Experiment 1—Main effects of factors on variance of total shortage levels

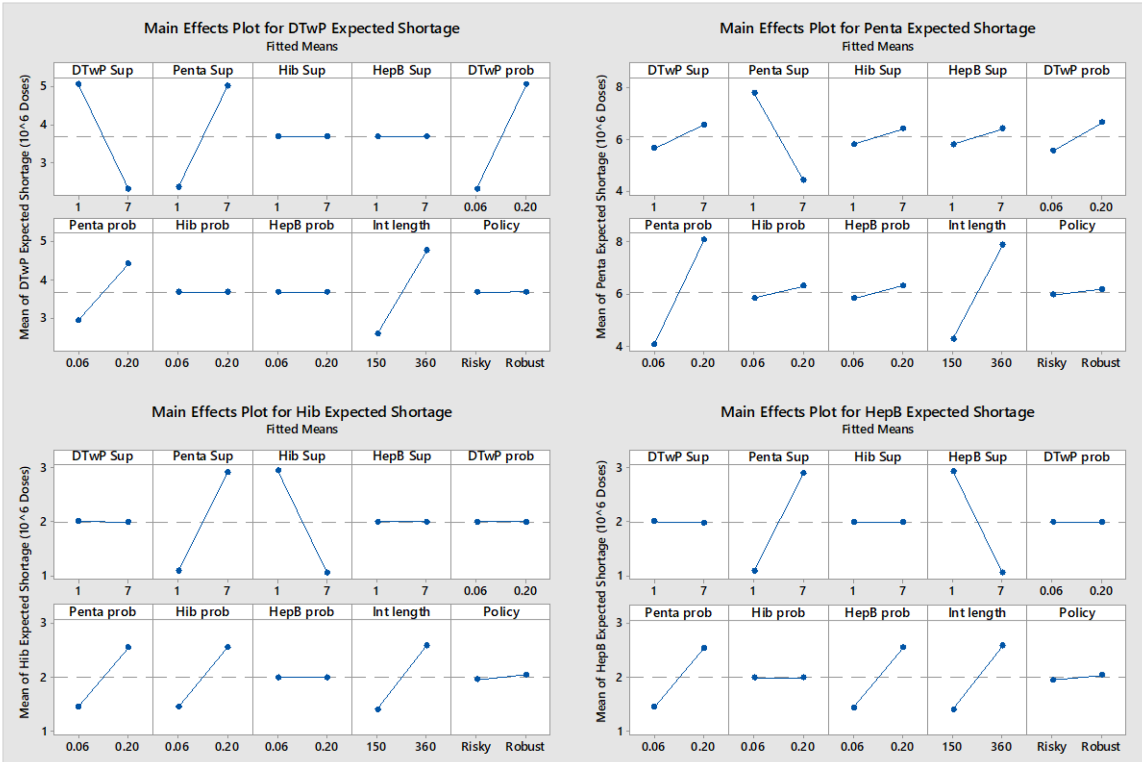


Figure 4: Experiment 1—Main effects of factors on individual vaccine expected shortage levels

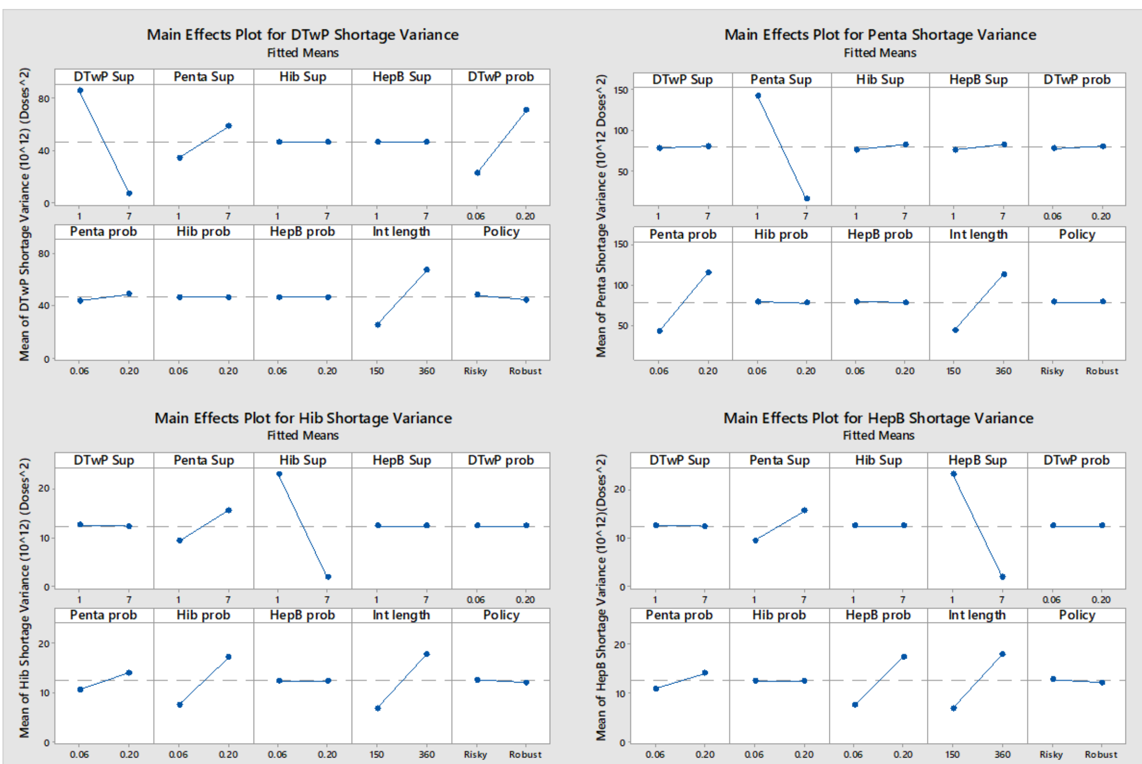


Figure 5: Experiment 1—Main effects of factors on individual vaccine variance of shortage

We also analyzed the variance of individual vaccine shortage and the variance of shortage across all vaccines. Figure 3 represents the main effects of factors on the variance of total shortage levels. As the number of suppliers of a vaccine increases, the total variance of the shortage across all vaccines decreases. Figure 5 shows a variance of an individual vaccine shortage. It can be seen that as the number of suppliers of the vaccine under consideration increases, there is a decrease in the variance of shortage. However, with an increase in the number of suppliers of vaccines containing at least one similar antigen, there seems to be an increase in the variance of a shortage of the vaccine under consideration. For all the vaccines, as the probability of interruption and the mean interruption length increase, there is an increase in the variance of the vaccine shortage levels. There is no significant effect of stockpiling policy A or B on the variance of any vaccine shortage levels. There are, however, significant two-level interaction effects, which are shown in the figures A5 and A6 in the Appendix.

Next, we compare the results from all the three experiments—experiment 1 considering stockpiles of both combination and monovalent vaccines, experiment 2 considering of only monovalent vaccines, and experiment 3 considering only combination vaccines. We compare the expected shortage levels, the variance of the shortage levels, the expected shortage cost, and the variance of the shortage cost for the three experiments. Specifically, we test the following null and alternate hypotheses:

Null Hypothesis: $H_{o1} =$ Mean expected shortage levels are equal for all three experiments
Alternate Hypothesis: $H_{a1} =$ Mean expected shortage level for at least one experiment is not equal

Null Hypothesis: $H_{o2} =$ Mean variance of the shortage is equal for all three experiments
Alternate Hypothesis: $H_{a2} =$ Mean variance of the shortage for at least one experiment is not equal

Null Hypothesis: $H_{o3} =$ Mean expected cost of shortage is equal for all three experiments
Alternate Hypothesis: $H_{a3} =$ Mean expected cost of shortage for at least one experiment is not equal

Null Hypothesis: $H_{o4} =$ Mean variance of shortage cost is equal for all three experiments
Alternate Hypothesis: $H_{a4} =$ Mean variance of shortage cost for at least one experiment is not equal

We compare the shortage levels from the different experiments because countries have limited space in their cold-chain facilities, and knowing whether to stock combination and monovalent vaccines or just consider monovalent vaccines for safety stock affects the supply chain. Secondly, we also focus on comparing purchasing costs of vaccines for the expected shortage levels because a low cost will increase the affordability of the stockpiles for each country. The vaccine prices used in this study are shown in Table 6, which are the weighted average prices (WAP) for the year 2015 obtained from UNICEF [31],[32]. Generally, it can be seen that monovalent vaccines are less expensive than combination vaccines. The Hib vaccine is an exception in our case. Considering these vaccine price conditions, we would like to explore the optimal type of vaccine mix that would require the minimum cold-chain space as well as the minimum purchasing cost of vaccines in the stockpile.

Table 6: Weighted average price (WAP) per dose for vaccines under study

Vaccine	DTwP	Penta	Hib	HepB
Price per dose (USD)	0.28	1.91	4.00	0.18

Source: [31],[32]

The box plot of the expected shortage levels, the variance of such shortages, the expected shortage costs, and variance of the shortage cost, respectively, for experiments 1, 2, and 3 are shown in Figure 6. We verify the null and alternate hypotheses stated above by using a 2-sample t-test. The confidence interval of the difference and the p-values obtained from the statistical tests for shortage levels are shown in Table 7, and in Table 8 shortage costs and variance are shown. It can be seen here that experiment 3 offers the least expected shortage levels, while experiment 2 results in the highest expected shortage levels. Also, the variance of shortage levels is largest for experiment 2, while for experiments 1 and 3, the variance is similar to each other. Given this, it is preferred not to use only monovalent vaccine stockpiles. When we compare the expected costs of shortage, it can be seen that all three experiments have similar expense levels. However, the variance of the shortage cost is higher for experiment 2. Thus, for the price per dose of vaccines used in this study, which are the actual prices of the four vaccines [31],[32], having only monovalent vaccines results in the highest purchasing cost.

Table 7: Confidence interval (CI) of difference and p-values for expected and variance of shortage levels

	Expected Shortage Level			Variance of Shortage		
		Expt 2	Expt 3		Expt 2	Expt 3
Expt 1	CI (Row - Col) 10^6 Doses	(-4.64, -1.49)	(1.51, 10.74)	CI (Row - Col) 10^{12} Doses^2	(-438.8, -245.7)	(-275, 344)
	P-values	0.000	0.016	P-values	0.000	0.798
Expt 2	CI (Row - Col) 10^6 Doses	NA	(4.50, 13.88)	CI (Row - Col) 10^{12} Doses^2	NA	(57, 697)
	P-values		0.002	P-values		0.026

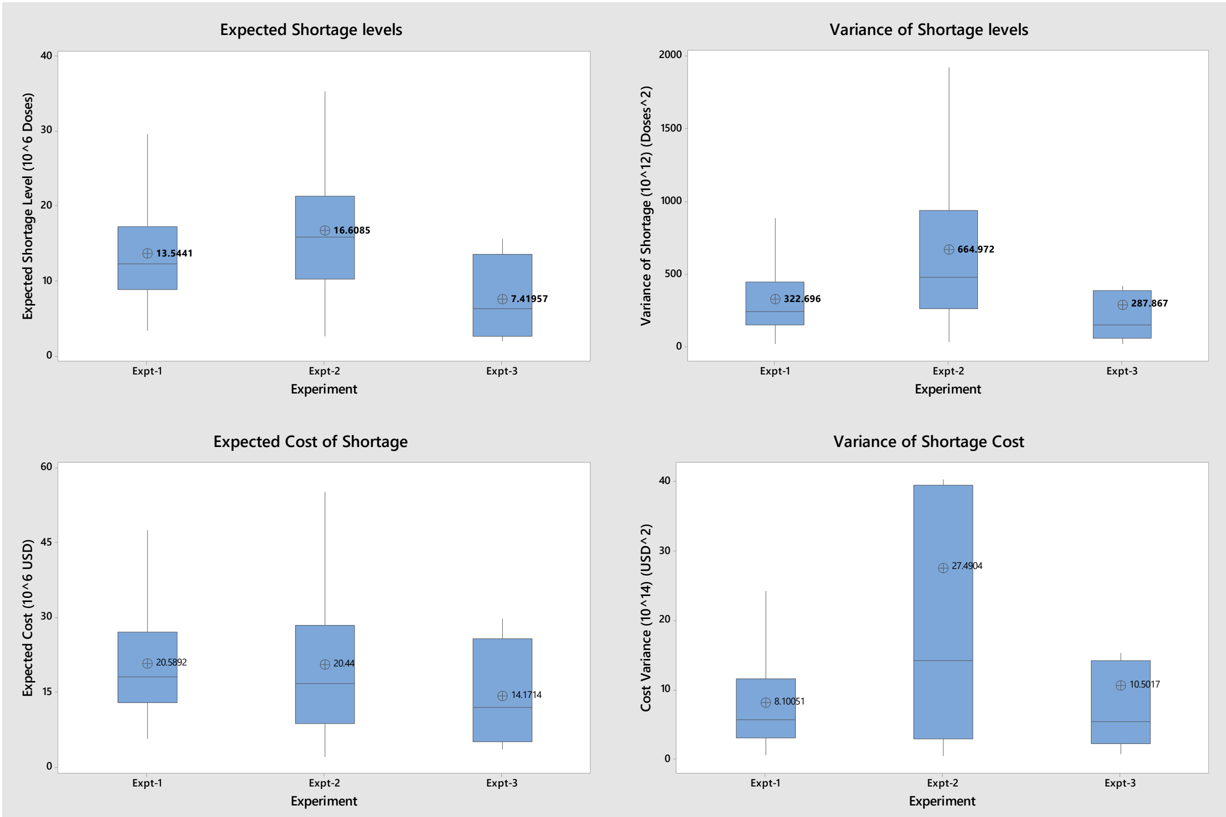


Figure 6: Box plot showing comparisons of each experiment type

Table 8: Confidence interval (CI) of difference and p-values for expected shortage cost and its variance

	Expected Cost of Shortage			Variance of Shortage Cost		
		Expt 2	Expt 3		Expt 2	Expt 3
Expt 1	CI (Row - Col) 10^6 USD	(-2.65, 2.95)	(-2.38, 15.21)	CI (Row - Col) 10^{12} USD^2	(-25.33, -13.45)	(-13.68, 8.87)
	P-values	0.916	0.128	P-values	0.000	0.630
Expt 2	CI (Row - Col) 10^6 USD	NA	(-2.78, 15.32)	CI (Row - Col) 10^{12} USD^2	NA	(4.85, 29.13)
	P-values		0.149	P-values		0.010

4.1.4 Simulation Study Summary

The simulation study shows that if we consider only expected shortage levels for the vaccine stockpiles, we leave a substantial amount of risk uncovered since the variance of a shortage is large. Therefore, stockpile levels should be determined by taking into account the variance of shortage levels as well. There is a significant effect of the key factors on the expected shortage levels and the variances. The expected shortages and the variances decrease when the number of suppliers of the vaccine under consideration increases. However, the expected shortage levels and their variance increase when the probability of interruption and the mean interruption length increase. Stockpiling policies of stocking either risky or robust vaccines do not have any significant effect on the expected shortage levels or the variance of shortage. Also, it is not recommended to have only monovalent vaccines in the stockpile as it would incur a high expected shortage and high shortage variances. For the price conditions considered in this study, the expected shortage cost is highest when we have only monovalent vaccines in the stockpile.

4.2 Tractable Model

The need to allow those responsible for vaccine inventories across the globe to easily analyze and control their safety stock results in the need for tractable safety stock model that can be embedded in spreadsheets and can be easily used by policy makers without having to run the simulation. Furthermore, tractable safety stock models facilitate sensitivity analysis. Thereby we propose a tractable safety stock model assuming that it could be used as part of a continuous review stochastic inventory system such as $(R_v,\ Q_v)$ for each vaccine v.

Without loss of generality consider that R_v corresponds to the re-order inventory level that triggers an order of size Q_v to be placed. SS_v is the safety stock of vaccine $v \epsilon V$. I_l is the random interruption length for the supply of given vaccine v. l is a constant for the delivery time of vaccines from the manufacturer to its destination.

When the inventory level reaches a re-order point R_v for a vaccine, a fixed order quantity Q_v is placed during the regular supply of vaccines. The inventory satisfies the expected lead-time demand during the time between placing the order up to its receipt. In some cases, if the order arrives late due to any given reason, the safety stock can be used for mitigating the shortage. However, when the supply interruption of random length I_l occurs, the vaccines will be supplied from the safety stock until the suppliers are back to full production. Thus, the focus of this study is to determine the safety stock SS_v of vaccines, while determining the order quantity Q_v is not in the scope of this study. It is assumed that when a supply interruption occurs for a given vaccine, the stockpile is determined for all the vaccines supplying antigens similar to the vaccine in shortage such that their stockpiles together satisfy the expected antigen shortages. Thus, the SS_v shown in Figure 6 represents the safety stock of vaccine v when a supply interruption for the same vaccine v or any of the vaccines supplying similar antigens has occurred.

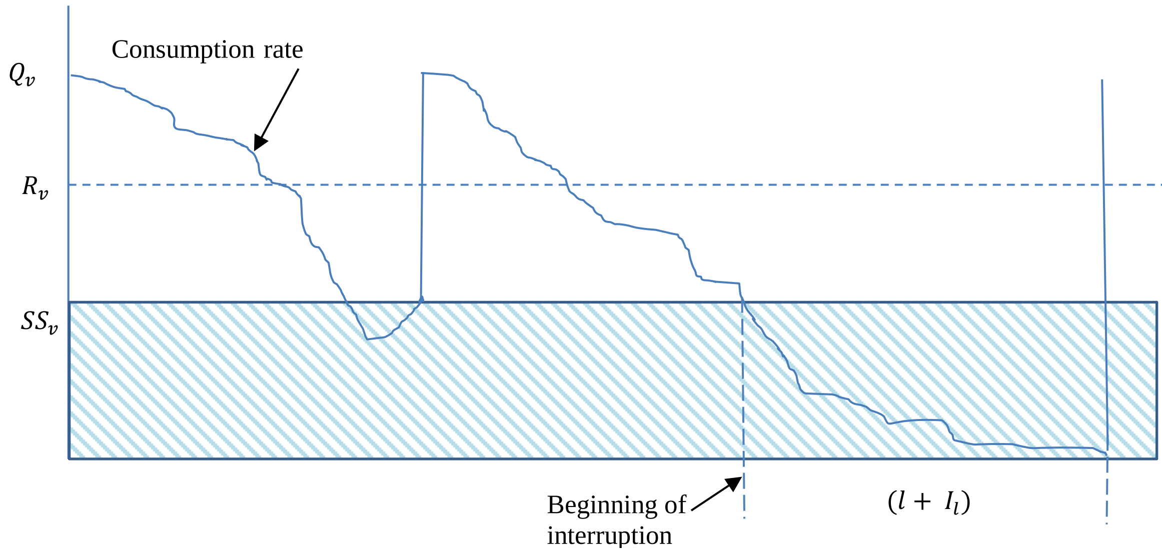


Figure 7: Continuous review stochastic inventory model for vaccine stockpiles

We consider that there are m_v suppliers for each vaccine with the probability of supply interruption as p_v. It is the same for all the suppliers of a given vaccine. For a given vaccine, any number of suppliers N_v out of the available m_v can face a supply interruption. Thus, N_v can take discrete values ranging from 0 to m_v, where all suppliers for a given vaccine have an equal probability of facing supply interruption p_v. Therefore, N_v is binomially distributed with parameters $N_v \sim B(m_v, p_v)$. The interruption length I_l is also considered as a random variable with known distribution parameters. Additionally, the safety stock must offer a service level of α so that the probability that a stockout will not happen during the supply interruption lead-time is α%. The interruption lead-time consists of a constant time l to distribute vaccines to the destination in addition to the random interruption length I_l.

4.2.1 Formulation of Safety Stock Model

Let us consider following notations for the sets, the parameters, and the variables.

Sets:

A: Set of antigens
V: Set of vaccines
A_v: Set of antigens supplied by vaccine $v \in V, A_v \subset A$
V_a: Set of vaccines supplying antigen $a \in A, V_a \subset V$

Parameters:

Sup_v: Total supply of vaccine $v \in V$ per day across all suppliers
m_v: Number of suppliers of vaccine $v \in V$
p_v: Probability of supply interruption at suppliers of vaccine $v \in V$
φ_{va}: Fraction of antigen $a \in A$ demand supplied by vaccine $v \in V$
l : Constant for the delivery time of vaccines from manufacturer to destination once supply is restored

Variables:

I_l : $r.v$ Interruption length following a known distribution with mean μ_{I_l} and standard deviation σ_{I_l}
N_v: $r.v$ Number of suppliers of vaccine $v \in V$ out of m_v facing supply interruption over a year. Given that probability of interruption at vaccine supplier is p_v , hence, $N_v \sim B(m_v, p_v)$

$E[N_v]$: $m_v p_v$

$V[N_v]$: $m_v p_v (1 - p_v)$

K_v: $r.v$ Supply shortage levels of vaccine $v \in V$ when vaccine v faces supply interruption
D_a: $r.v$ Lead-time demand for antigen $a \in A$ across all vaccines facing interruption
D_v: $r.v$ Lead-time demand for vaccine $v \in V$ due to any common antigen supplying vaccines facing interruption

In the first step, we determine K_v the supply shortage of vaccine v that is itself facing a supply interruption of length $(l + I_l)$. K_v is a product of total supply of vaccine v per day per supplier, the number of suppliers facing supply interruption, and the lead-time.

$$K_v = \frac{Sup_v}{m_v} . N_v . \ (l + I_l) \qquad (6)$$

As N_v and I_l are random variables, the expected supply shortage and its variance for a vaccine v facing supply interruption correspond to (7) and (8), respectively [33],[34].

$$E[K_v] \ = \ E\left[\frac{Sup_v}{m_v} N_v (l + \ I_l)\right]$$

$$= \ E\left[\frac{Sup_v}{m_v} N_v\right] . E[(l + \ I_l)]$$

as

$$E\left[\frac{Sup_v}{m_v} N_v\right] = \frac{Sup_v}{m_v} . E[N_v] \, ,$$

and

$$E[l + \ I_l] = l + E[I_l] \ \ ,$$

then

$$E[K_v] = \frac{Sup_v}{m_v}.E[N_v].\ (l + E[I_l])\ \ . \qquad (7)$$

Variance of K_v is given by

$$V[K_v]\ =\ V\left[\frac{Sup_v}{m_v}N_v(l +\ I_l)\right]$$

$$V[K_v] =\ \frac{Sup_v^2}{m_v^2}.\ V[N_v.(l +\ I_l)]$$

$$V[K_v] =\ \frac{Sup_v^2}{m_v^2}.\ \left(E\left[\left(N_v.(l +\ I_l)\right)^2\right]\ -\ (E[N_v.(l +\ I_l)])^2\right)$$

$$V[K_v] =\ \frac{Sup_v^2}{m_v^2}.\ \left((E[N_v^2].E[(l +\ I_l)^2]) -\ \left(\left[E[N_v]\right]^2.[E[(l +\ I_l)]\ ]^2\right)\right)$$

As

$$E[N_v^2] =\ V[N_v] +\ E[N_v]^2\ \text{ and } E[(l +\ I_l)^2] =\ V[l +\ I_l] +\ E[l +\ I_l]^2,$$

then

$$V[K_v] =\ \frac{Sup_v^2}{m_v^2}.\left((V[N_v] +\ E[N_v]^2).(V[l +\ I_l] +\ E[l +\ I_l]^2)\ -\left(\left[E[N_v]\right]^2.[E[(l +\ I_l)]\ ]^2\right)\right).$$

Expanding the terms

$$V[K_v] =\ \frac{Sup_v^2}{m_v^2}.\Big(V[N_v].V[l +\ I_l] + V[N_v].E[l +\ I_l]^2 +\ E[N_v]^2.V[l +\ I_l] + \cancel{E[N_v]^2.E[l +\ I_l]^2}$$
$$- \cancel{\left(\left[E[N_v]\right]^2.[E[(l +\ I_l)]\ ]^2\right)}\Big),$$

since $V[l +\ I_l] = \mathrm{V}[I_l]\ and\ E[l +\ I_l] = l + E\ [I_l]$, then

$$V[K_v] =\ \frac{Sup_v^2}{m_v^2}.(V[N_v].V[I_l] + V[N_v].E[l +\ I_l]^2 +\ E[N_v]^2.V[I_l]) \qquad (8)$$

In the second step, we determine the expected antigen lead-time demand and its variance as a consequence of the vaccine supply shortages. Thus, the expected lead-time demand of each antigen corresponds to the sum of the supply shortages across all the vaccines containing the given antigen. Similarly, the variance of the antigen lead-time demand is the sum of the variances of all the vaccines supplying the given antigen.

$$E[D_a] = \sum_{v\,\epsilon\,V_a} E[K_v] \qquad \forall\ a\ \in A \qquad (9)$$

$$V[D_a] = \sum_{v\,\epsilon\,V_a} V[K_v] \qquad \forall\ a\ \in A \qquad (10)$$

Finally, in the third step, we determine the expected lead-time demand and its variance for vaccines containing antigens similar to those of the vaccines facing supply interruption. Thus, the vaccine expected lead-time demand and its variance are a function of the antigen lead-time demand and variance.

Since more than one vaccine supplies a given antigen, we estimate φ_{va}, the fraction of antigen $a \in A$ demand supplied by vaccine $v \in V$, which is shown in (3).

When a vaccine v supplies multiple antigens, we determine the fraction of expected antigen demand to be supplied by the given vaccine for each antigen contained in that vaccine. Let a be the antigen for which the vaccine v needs to supply the highest expected number of doses. It is represented by the following expression:

$$a = \underset{a_1}{\mathrm{Arg}}\left(\max\left\{\varphi_{va_1}.E\left[D_{a_1}\right] \mid a_1 \epsilon A_v\right\}\right).$$

Then the expected vaccine lead-time demand $E[D_v]$ and its variance $V[D_v]$ must account for largest antigen shortage,

$$E[D_v] = \varphi_{va}.E[D_a] \qquad (11)$$

$$V[D_v] = \varphi_{va}^2.\ V[D_a] \qquad (12)$$

Now, we determine the safety stock that ensures a desired service level α. By its definition the probability of having no stockouts during interruption lead-time is equal to α%,

$$P(D_v \leq R_v) = \alpha = \text{Probability of no stockout during leadtime} \quad , \qquad (13)$$

where inventory re-order level corresponds to

$$R_v = E[D_v] + SS_v \quad \text{where } SS_v = \text{Safety Stock of vaccine} \quad . \qquad (14)$$

Subtracting $E[D_v]$ from both sides of inequality in (13) and dividing by σ_{D_v} obtained from (12) we obtain

$$P\left(\frac{D_v - E[D_v]}{\sigma_{D_v}} \leq \frac{R_v - E[D_v]}{\sigma_{D_v}}\right) = \alpha.$$

By the central limit theorem and the definition of a standardized normal variable,

$$P\left(Z \leq \frac{SS_v}{\sigma_{D_v}}\right) \leq \alpha$$

$$SS_v = Z_\alpha\sqrt{V[D_v]}$$

Substituting $V[D_v]$ from (12)

$$SS_v = Z_\alpha \sqrt{\varphi_{va}^2 . V[D_a]} \qquad (15)$$

(15) corresponds to the safety stock that will ensure α% service level during the interruption. Similarly, we can define the re-order level at which orders must be placed when the system does not face supply interruption,

$$R_v = \varphi_{va} . E[D_a] + Z_\alpha \sqrt{\varphi_{va}^2 . V[D_a]}$$

5. Model Validation

To validate the tractable safety stock model as shown in (15), we will compare its results with the simulation results for the same experimental scenarios performed in the simulation study. To perform this comparison, we will use distributions and input parameters similar to those we used for the simulated experimental scenario.

We follow a truncated normal distribution for the interruption length, as used in the simulation study. From the mean and standard deviation of normal distribution denoted by $N(\mu_{I_l}, \sigma_{I_l})$ we determine the mean and standard deviation of truncated normal distribution $N_T(\mu_{tI_l}, \sigma_{tI_l})$ by using following equations:

$$\mu_{tI_l} = \mu_{I_l} + \sigma_{I_l} . \frac{\phi\left({}^{-\mu_{I_l}}/_{\sigma_{I_l}}\right)}{1 - \Phi\left({}^{-\mu_{I_l}}/_{\sigma_{I_l}}\right)}$$

$$\sigma_{tI_l}^2 = \sigma_{I_l}^2 . \left(1 + \left(\frac{-\mu_{I_l}}{\sigma_{I_l}} . \phi\left({}^{-\mu_{I_l}}/_{\sigma_{I_l}}\right) \Big/ 1 - \Phi\left({}^{-\mu_{I_l}}/_{\sigma_{I_l}}\right) \right) - \left(\phi\left({}^{-\mu_{I_l}}/_{\sigma_{I_l}}\right) \Big/ 1 - \Phi\left({}^{-\mu_{I_l}}/_{\sigma_{I_l}}\right) \right)^2 \right),$$

where

$\phi(\ \ )$: Probability Density Function (p.d.f) of normal distribution

$\Phi(\ \ )$: Cumulative Density Function (c.d.f) of normal distribution

Thus, if we substitute the mean and variance of I_l following truncated normal distribution and N_v following binomial distribution, the expressions (7) and (8) for $E[K_v]$ and $V[K_v]$ are given by

$$E[K_v] = \frac{Sup_v}{m_v}.\ m_v p_v.\left(l + \mu_{tI_l}\right)$$

$$V[K_v] = \frac{Sup_v^2}{m_v^2}\left\{m_v p_v(1-p_v).\ \sigma_{tI_l}^2 + m_v p_v(1-p_v).\left(l + \mu_{tI_l}\right)^2 + (m_v p_v)^2.\sigma_{tI_l}^2\right\}.$$

Then, the expected antigen lead-time demand and variance remain the same as (9) and (10)

$$E[D_a] = \sum_{v \in V_a} E[K_v]$$

$$V[D_a] = \sum_{v \in V_a} V[K_v]\ .$$

The expected vaccine lead-time demand and variance are as given by (11) and (12)

$$E[D_v] = \varphi_{va}.E[D_a]$$

$$V[D_v] = \varphi_{va}^2.\ V[D_a]\ ,$$

where

$$a = \underset{a_1}{\mathrm{Arg}}\left(\max\left\{\varphi_{va_1}.E\left[D_{a_1}\right] \mid a_1 \in A_v\right\}\right).$$

We use the above expressions and obtain the stockpile level for the shortage scenarios described in experiment 1 (refer to section 4.1.2.1) without considering stockpiling policy as one of the experimental factors since it has no effect on the vaccine shortage level, as seen in the simulation study. Now, from the simulation study, we obtain the expected vaccine shortages and their variance for each experimental scenario of experiment 1. The expected vaccine shortage from the simulation can also be termed as the expected vaccine lead-time demand during the interruption, and thus the computed shortage variance can be used in expression (15) to obtain the safety stock of vaccines for those simulated experimental scenarios. Thus, we have the expected vaccine lead-time demand and stockpile levels from two different approaches, and we compare them using a 2-sample t-test. Table 9 summarizes the results of the 2-sample t-test for each vaccine. The null and alternate hypotheses that we want to test are as follows:

$$H_{05}\text{: Mean of } [E[D_v]]_{simulation} = \text{Mean of } [E[D_v]]_{inventory\ model}$$
$$H_{a5}\text{: Mean of } [E[D_v]]_{simulation} \neq \text{Mean of } [E[D_v]]_{inventory\ model}$$

$$H_{06}\text{: Mean of } [E[SS_v]]_{simulation} = \text{Mean of } [E[SS_v]]_{inventory\ model}$$
$$H_{a6}\text{: Mean of } [E[SS_v]]_{simulation} \neq \text{Mean of } [E[SS_v]]_{inventory\ model}$$

Table 9: Summary of 2-sample t-test comparison of expected lead-time demand and safety stock of vaccines

Vaccine	Expected Lead-time Demand (Million Doses)					Safety Stock (Million Doses)				
	Tractable Model	Simulation	Difference	Confidence Interval	P-value	Tractable Model	Simulation	Difference	Confidence Interval	P-value
DTwP	3.6	3.67	0.07	(-0.44, 0.30)	0.710	6.64	6.96	-0.322	(-0.99, 0.35)	0.345
Penta	4.74	5.97	-1.229	(-1.65, -0.81)	0.000	8.43	9.46	-1.021	(-1.78, -0.27)	0.008
Hib	1.92	1.95	-0.032	(-0.26, 0.19)	0.780	3.39	3.56	-0.168	(-0.51, 0.18)	0.338
HepB	1.92	1.95	-0.028	(-0.25, 0.19)	0.803	3.39	3.58	-0.19	(-0.54, 0.15)	0.279

From the statistical comparison shown in Table 9, we can see that the expected lead-time demand and the safety stock levels of all the three vaccines, DTwP, Hib, and HepB, match very well with the simulation results. However, the penta vaccine's expected lead-time demand and the safety stock from the tractable model seem underestimated. We plotted a scatterplot of the safety stock levels from the simulation on X-axis and the tractable model on the Y-axis with a line of equality at a 45-degree angle (refer to Figure 8) for the same experimental scenarios. It can be seen that the stockpile levels from the tractable model and the simulation study are aligned along the line of equality for all three vaccines. However, for the penta vaccine, the stockpile levels deviate away from the line of equality, showing the differences in the tractable model and the simulation results. The underestimation of the stockpile levels from the tractable model is observed only for combination vaccines, which means an evaluation of the vaccine's expected lead-time demand and its variance (refer to (11) and (12)) when the vaccine is supplying more than one antigen, provides lower values than the simulation results. The deviation from the equality line is smaller when the stockpile levels are low; however, the deviation seems to be amplified as the stockpile levels are increased.

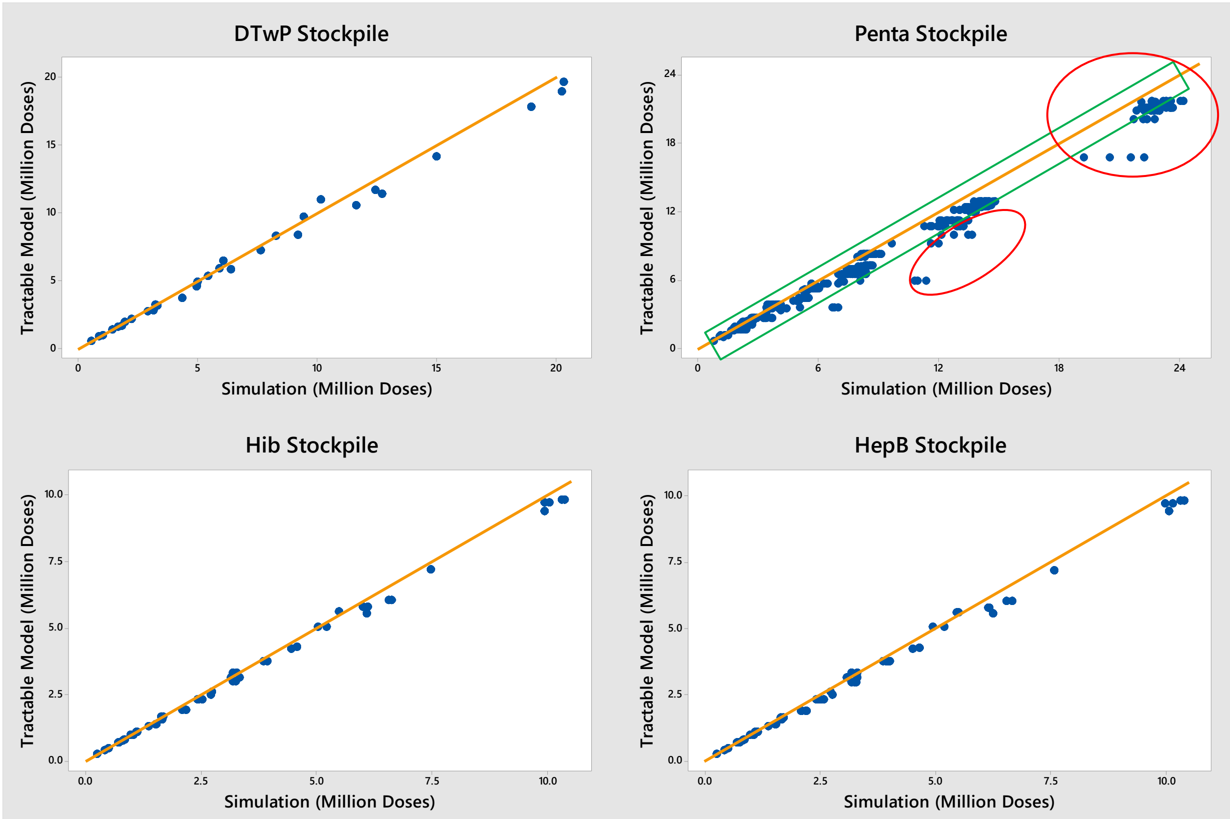


Figure 8: Scatterplot with line of equality—comparing stockpile levels from simulation study and tractable model

Applying the tractable safety stock model to the same scenarios used in experiments 1, 2, and 3 from our simulation study, we compare the stockpile levels for different types of vaccine mixes (refer to sections 4.1.2.1, 4.1.2.2, and 4.1.2.3). We evaluate the safety stock levels for having both combination and monovalent vaccines together in the safety stock, only monovalent vaccines, and only combination vaccines, respectively. Figures 9 shows the boxplot of the stockpile levels and the cost of purchasing such stockpiles for each type of the vaccine mix. Boxplot of stockpile levels illustrates that having only monovalent vaccines results in the highest stockpile levels as compared with the other two vaccine mixes. Therefore, it is preferable not to have stockpiles that constitute only monovalent vaccines since it puts excessive pressure on the cold-chain needs. Additionally, with the price of vaccines used in this study, the purchasing cost is highest for the monovalent vaccine stockpiles. Thus, monovalent vaccine stockpiles are also not an adequate choice when we look at things from the cost perspective.

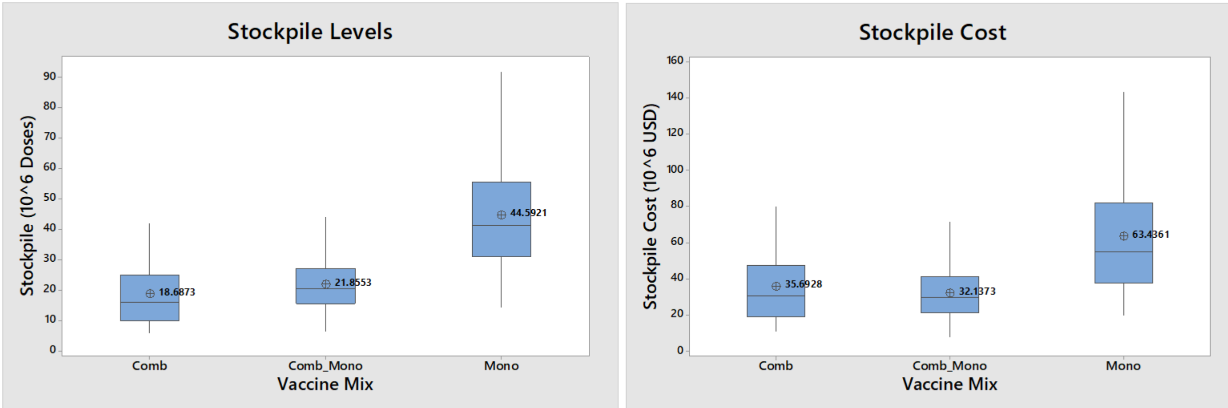


Figure 9: Stockpile levels and stockpile cost comparison for different vaccine mixes

The purchasing costs of vaccines in stockpiles with only combination vaccines and with a mix of combination and monovalent vaccines are statistically the same. The results of the 2-sample t-test in Table 10 shows that the differences in stockpile levels and cost are statistically insignificant for stockpiles with only combination vaccines and stockpiles with a mix of combination and monovalent vaccines.

Table 10: 2-sample t-test results for stockpile levels and stockpile cost

	Comb	Comb_Mono	Difference	Confidence Interval	P-values
Stockpile Levels (M Doses)	18.68	21.86	-3.17	(-12.92, 6.58)	0.468
Stockpile Cost (M USD)	35.69	32.14	3.55	(-15.06, 22.17)	0.665

To evaluate the price conditions under which having only monovalent vaccines in the stockpile would be a preferred option, we performed a cost analysis by varying the price of the monovalent vaccine Hib as USD 0.64 per dose instead of USD 4.00. The graphical analysis of the stockpile cost with the new price for the Hib vaccine is shown in Figure 10. The stockpile cost of monovalent vaccines became as attractive as those of the other two safety stock configurations. However, as we observed in Figure 9, the stockpile quantity for monovalent vaccines is rather high. The stockpile levels with only combination vaccines and with a mix of combination and monovalent vaccine are similar, but under the revised price conditions of monovalent vaccines, the cost of a stockpile with a mix of combination and monovalent vaccines is much lower than that of a stockpile with only combination vaccines. Therefore, it is preferred to have a stockpile of a mix of combination and monovalent vaccines to facilitate lower stockpile levels and lower cost investment.

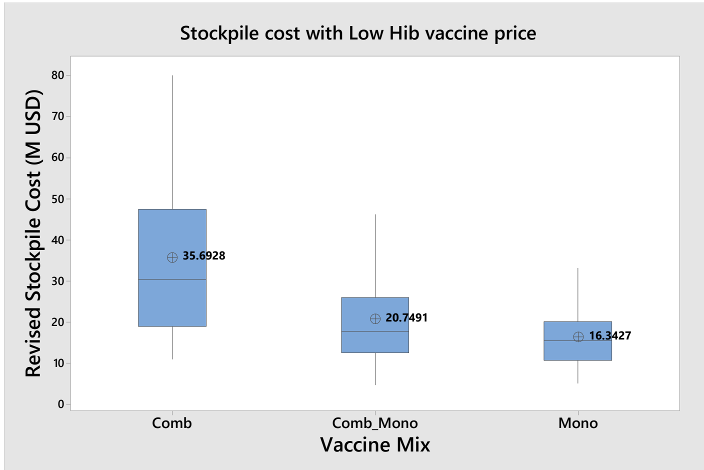


Figure 10: Revised stockpile cost for each type of vaccine mix with Hib price as USD 0.64

6. Conclusion

The tractable safety stock model developed in this study can be used to determine the stockpile levels for any of the combination or monovalent vaccines with multiple suppliers, varying likelihoods of supply interruption, and random interruption lengths.

Three out of the four key factors considered in the study affect the safety stock levels significantly. The stockpile level decreases with an increase in the number of suppliers of the vaccine. However, it increases when the probability of interruption at the suppliers or the mean interruption length increases. The stockpile levels are not affected when we switch from the policy to stockpile risky vaccines to the policy to stockpile robust vaccines.

The analysis of stockpile quantity and the stockpile purchasing cost for different types of vaccine mixes shows that it is preferred to have stockpiles with a mix of combination and monovalent vaccines since this results in lower stockpile levels as compared to having only monovalent vaccine stockpiles and lower purchasing costs as compared to having only combination vaccine stockpiles.

The tractable inventory model allows one to perform a sensitivity analysis with ease. Thus, this study can be extended to perform a sensitivity analysis to understand the range of the input parameters for which the stockpile levels would remain unchanged.

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Appendix:

Table A: List of examples for pediatric vaccine shortages in US

Vaccine	Start year	Duration (months)	Reason
Tetanus and Diphtheria toxoids/Tetanus Toxoid (Td/TT)	November, 2000	**19**	Change in manufacturing process, manufacturer leaving market
Diphtheria and Tetanus toxoids and acellular Pertussis vaccine (DTaP)	March, 2001	**17**	Change in manufacturing process, manufacturer leaving market
Measles, Mumps and Rubella vaccine (MMR)	October, 2001	**10**	Change in manufacturing process
Varicella (VAR)	October, 2001	**11**	Change in manufacturing process
Pneumococcal Conjugate Vaccine (PCV)	August, 2001	**22**	Manufacturer upgrading filling line
Pneumococcal Conjugate Vaccine (PCV)	December, 2003	**10**	Manufacturer upgrading filling line
Pneumococcal Conjugate Vaccine (PCV)	February, 2004	**7**	
Meningococcal conjugate vaccine (MCV4)	June, 2005	**3**	High Demand
Meningococcal conjugate vaccine (MCV4)	June, 2006	**3**	High Demand
Hepatitis A	July, 2007	**9**	
Haemophilus Influenzae type b vaccine (Hib)	December, 2007	**19**	Manufacturer recalled lots of vaccines both monovalent and combination doses
Diptheria and Tetanus toxoids and acellular Pertusis vaccine (DTaP)	April, 2012	**18**	Manufacturer cannot meet demand requirements
Hepatitis A and varicella	January 2016		Payment problems

Table B: [24], [25]Low Income and Lower Middle Income countries of WHO Africa region

Sr No	**Countries**
1	Benin
2	Burkina Faso
3	Burundi
4	Cabo Verde
5	Cameroon
6	Chad
7	Côte d'Ivoire
8	Eritrea
9	Ethiopia
10	Ghana
11	Guinea
12	Kenya
13	Lesotho
14	Liberia
15	Madagascar
16	Malawi
17	Mali

18	Mauritania
19	Mozambique
20	Rwanda
21	Senegal
22	Sierra Leone
23	South Sudan
24	Swaziland
25	Togo
26	Uganda
27	Zambia
28	Zimbabwe

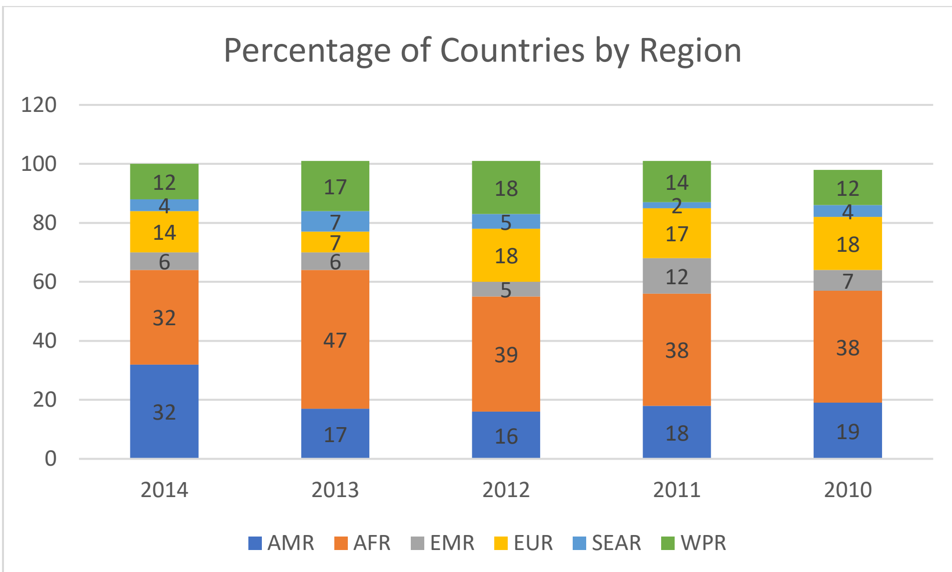

Figure A1: Percentage of countries by WHO region facing stockout (2010-2014)

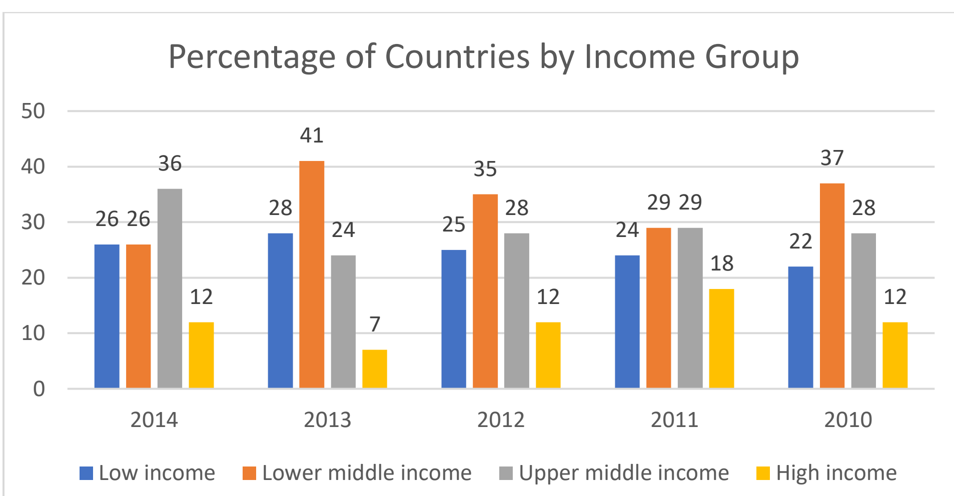

Figure A2: Percentage of countries by Income group facing the vaccine shortages

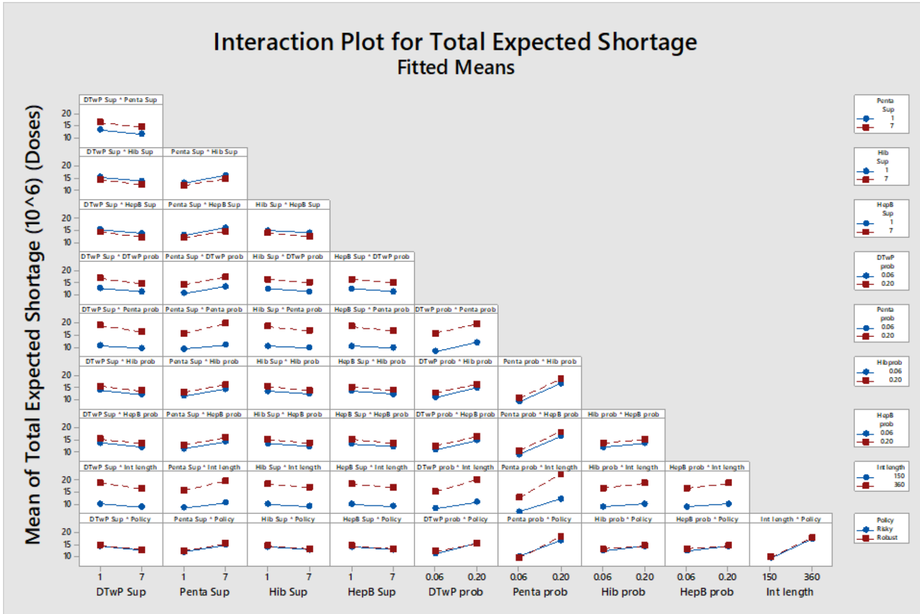

Figure A3: Experiment 1- Interaction effects of factors on total expected shortage levels

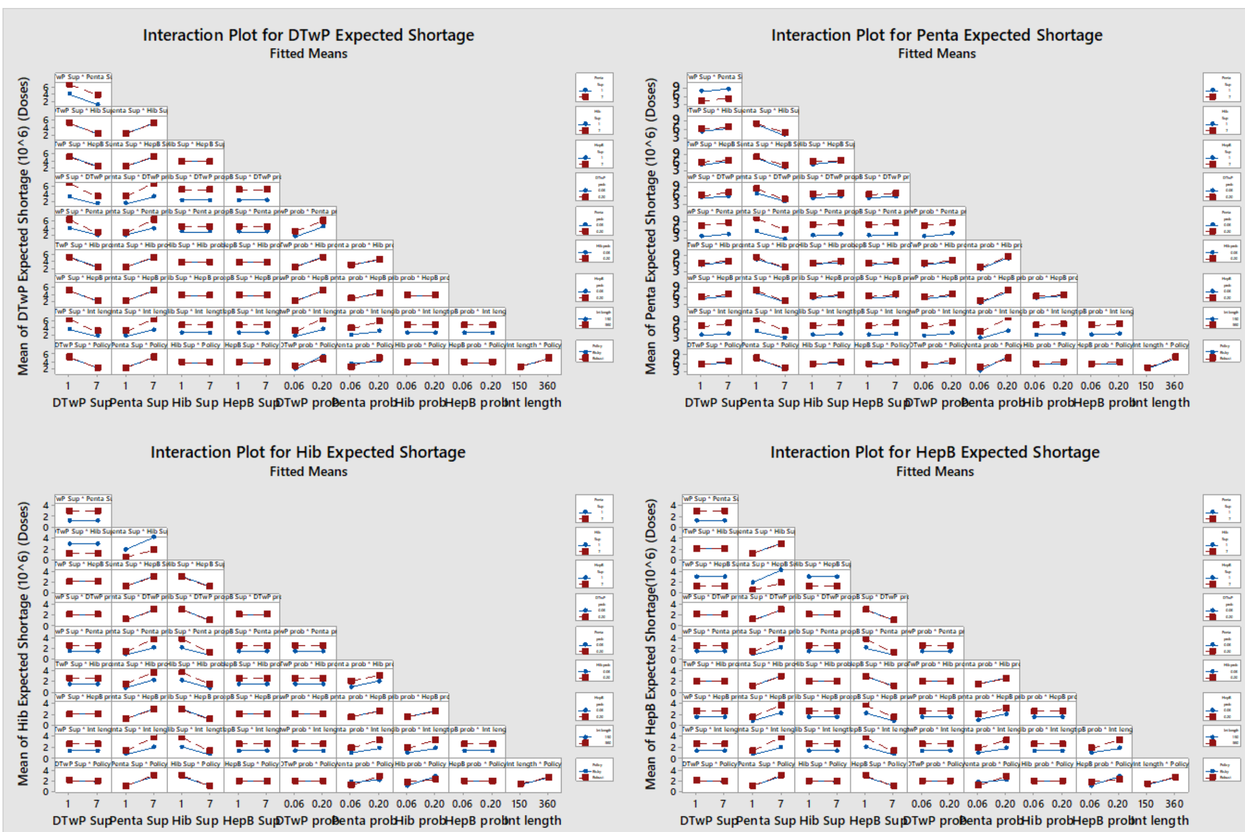

Figure A4: Experiment 1 - Interaction effects of factors on individual vaccine expected shortage levels

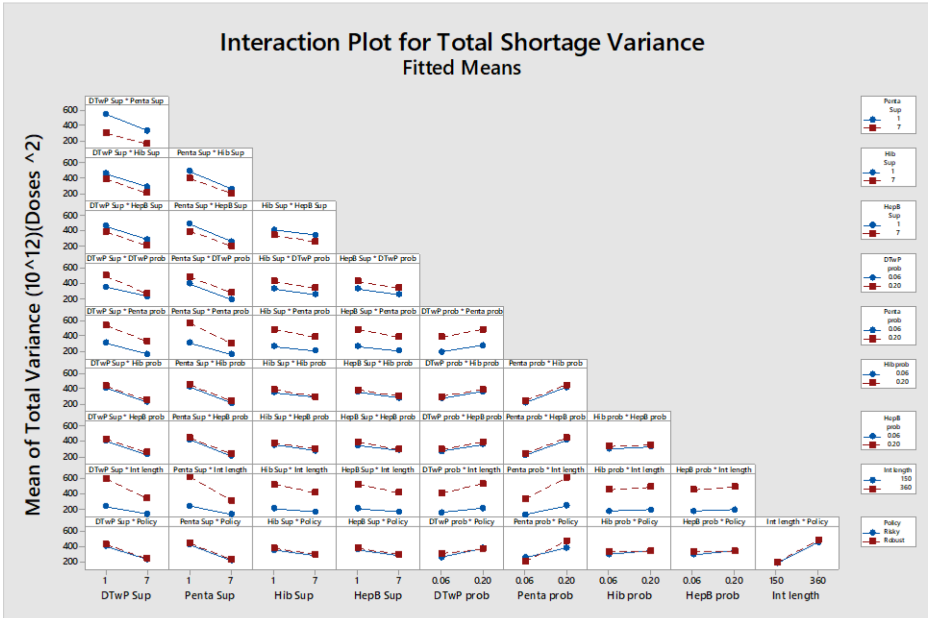

Figure A5: Experiment 1- Interaction effects of factors on total shortage variance

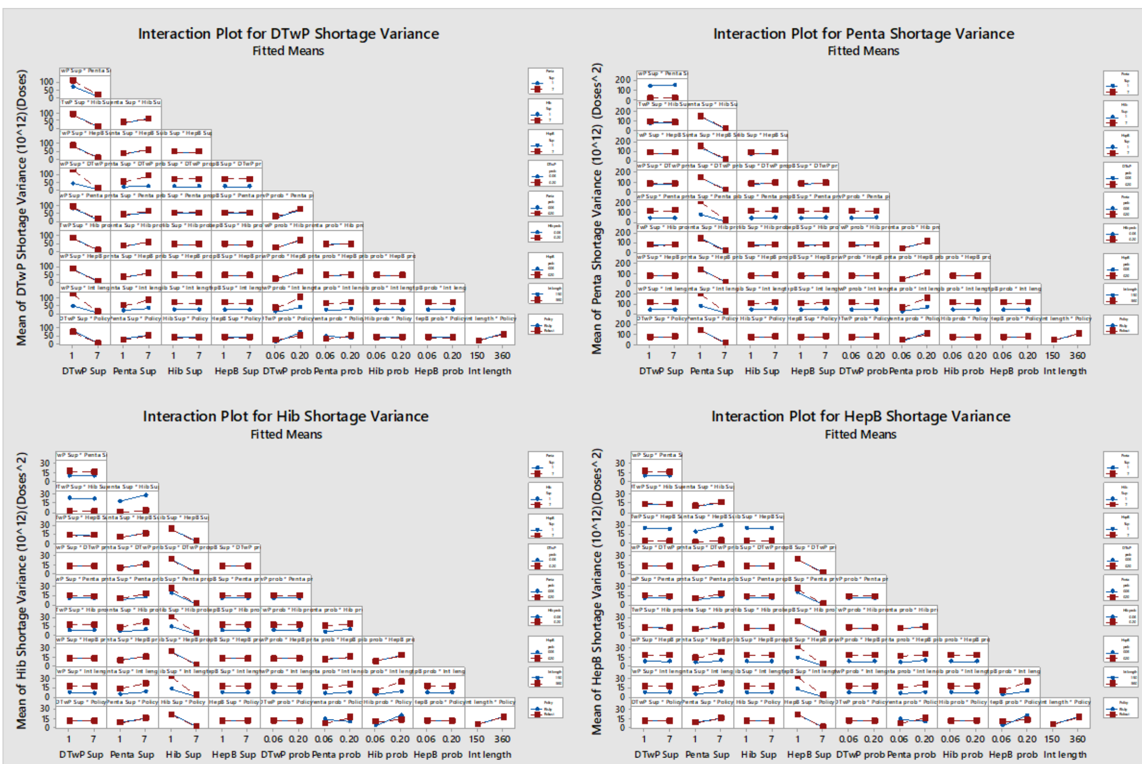

Figure A6: Experiment 1- Interaction effects of factors on individual vaccine shortage variance